Safety and Immunogenicity of a Recombinant Adenovirus Serotype 35-Vectored HIV-1 Vaccine in Adenovirus Serotype 5 Seronegative and Seropositive Individuals.

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Abstract

Background: Recombinant adenosine serotype 5 (rAd5)-vected HIV-1 vaccines have not prevented HIV-1 infection or disease and pre-existing Ad5 neutralizing antibodies may limit the clinical utility of Ad5 vectors globally. Using a rare Ad serotype vector, such as Ad35, may circumvent these issues, but there are few data on the safety and immunogenicity of rAd35 directly compared to rAd5 following human vaccination.

Methods: HVTN 077 randomized 192 healthy, HIV-uninfected participants into one of four HIV-1 vaccine/placebo groups: rAd35/rAd5, DNA/rAd5, and DNA/rAd35 in Ad5-seronegative persons; and DNA/rAd35 in Ad5-seropositive persons. All vaccines encoded the HIV-1 EnvA antigen. Antibody and T-cell responses were measured 4 weeks post boost immunization.

Results: All vaccines were generally well tolerated and similarly immunogenic. As compared to rAd5, rAd35 was equally potent in boosting HIV-1-specific humoral and cellular immunity and responses were not significantly attenuated in those with baseline Ad5 seropositivity. Like DNA, rAd35 efficiently primed rAd5 boosting. All vaccine regimens tested elicited cross-clade antibody responses, including Env V1/V2-specific IgG responses.

Conclusions: Vaccine antigen delivery by rAd35 is well-tolerated and immunogenic as a prime to rAd5 immunization and as a boost to prior DNA immunization with the homologous insert. Further development of rAd35-vected prime-boost vaccine regimens is warranted.

Keywords: HIV Vaccine; Adenovirus 35; Adenovirus 5; DNA vaccine; Randomized clinical trial

Introduction

The development of a safe and effective preventive HIV vaccine remains an urgent public health priority in the setting of an estimated 2.1 million new infections globally [1]. Since the first preventive HIV vaccine candidate entered clinical testing in 1987, four distinct vaccine concepts including subunit protein, DNA, and viral vector vaccines have been evaluated in six completed efficacy trials [2-7]. Thus far, only one vaccine regimen, a canarypox vector encoding three HIV-1 genes with a gp120 subunit boost, demonstrated partial efficacy in a phase 2b study [6]. Subsequent findings indicated that non-neutralizing IgG antibody responses to HIV-1 Env V1/V2 were significantly correlated with decreased risk of infection in vaccines [8].

HIV vaccine candidates using recombinant adenosine (rAd) vectors have been some of the most immunogenic [9]. The Step study (HIV Vaccine Trials Network [HVTN] 502) was the first efficacy trial to test an rAd5-vected vaccine expressing HIV-1 clade B Gag, Pol and Nef; however the product failed to protect against infection or disease progression. Furthermore, this study suggested that pre-existing Ad5 neutralizing antibodies may have played a role in increased HIV susceptibility among vaccines [4,10]. A multiclade/multigene DNA prime, rAd5 boost regimen encoding HIV-1 Gag, Pol, and Nef from
Subjects, Materials and Methods

Vaccines

All vaccines tested in HVTN 077 were produced by the NIH VRC and GenVec, Inc. (Gaithersburg, Maryland). One prototype vaccine consisted of a single E1-deleted, replication-deficient group B rAd35 vector, constructed to express a truncated modified HIV-1 clade A Env. The full E1, E3 and partial E4 deleted replication-deficient recombinant group C Ad5 vector also expressed the same truncated modified version of the HIV-1 clade A env gene. Both vaccines were formulated at a dose of 1 x 10^9 particle units and administered by needle and syringe intramuscularly.

The DNA-EnvA vaccine encodes for the clade A env gene and is one of the 6 plasmids included in HVTN 505 regimen [7]. The DNA vaccination was administered intramuscularly via the needle free injection device Biojector* 2000 (Tualitin, Oregon) at a dose of 4mg. The placebos for the adenovectors and DNA vaccines were final formulation buffer and phosphate-buffered saline (PBS), respectively.

Study design and procedures

HVTN 077 was a randomized, double-blind, placebo-controlled phase 1b trial conducted at 11 clinical sites in the United States. The protocol was approved by the institutional review boards of all participating centers (ClinicalTrials.gov registration NCT00801697). Between February of 2009 and January 2010, 192 adults aged 18-50 who reported low risk for infection and determined to be HIV-1-seronegative and healthy based on medical history, physical exam, and laboratory tests were enrolled after providing written informed consent. Eligible individuals who consented and enrolled were randomized to one of four treatment (T) groups (Table 1). Individuals randomized to treatment groups 2 (DNA/rAd5) or 3 (DNA/rAd35) were blinded to their assignment. For all groups, participants were blinded to assignment to vaccine or placebo. All participants were Ad35 neutralizing antibody (nAb) negative at baseline; for groups 1-3, participants were also Ad DNA nAb negative. In group 4, participants were Ad5 nAb positive determined by nAb titers ≥ 18.

Safety evaluations included physical examinations and standard clinical chemistry and hematological tests. Local injection site (pain, tenderness, redness, erythema, and induration) and systemic (malaise, headache, fever, chills, myalgias, arthralgias, nausea, vomiting, and fatigue) reactogenicity symptoms were assessed for three days following each vaccination or until resolution. Adverse events were graded based on the HVTN Table for Grading Severity of Adverse Experiences (http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_For_Grading_Severity_of_Adult_Pediatric_Events.pdf). Several licensed diagnostic HIV ELISA assays (Abbott HIVAB HIV 1/2[rDNA], Abbott Architect HIV Ag/Ab Combo, BioRad Genetic System HIV 1/2 Plus O ELA, BioRad Genetic System HIV 1/2 rLAV, and BioRad Multisport HIV-1/HIV-2 Rapid Test) were performed on sera at all participants at the end of study (Day 364) to assess vaccine-induced seroreactivity.

Blood samples for assessment for primary immunogenicity were collected at days 28 (4 weeks after the single rAd35 priming injection in Group 1), 84 (4 weeks after the DNA priming series in Groups 2-4) and 196 (4 weeks after the boost vaccination in all groups).

Immune response assays

Humoral responses

Neutralizing Antibodies to Ad5 and Ad35: Baseline Ad5 neutralizing antibody titers were measured as previously described with titers ≥ 18 noted as positive [24]. Ad35 neutralizing antibody titers were measured by luciferase transgene detection [25], and titers ≥ 12 noted as positive.

HIV-Specific Binding Antibody Assays: Validated binding antibody multiplex assays [26] for measurement of vaccine elicited

### Statistical analysis

All data from enrolled participants who received at least one vaccination were analyzed. Five study groups were evaluated for immunogenicity: the four vaccinated groups individually plus the pooled placebo group. HIV-1 specific IgG binding antibody and T-cell responses were evaluated at baseline (Day 0, IgG only) and at the primary immunogenicity timepoint, Day 196 (one month after the final injection). Rates of HIV-1 Env-specific antibodies and positive CD4+ and CD8+ T-cell responses (for cells expressing IFN-γ and/or IL-2 as measured by ICS) were estimated for each study group and timepoint. Lachenbruch's test was used for comparing primary immunogenicity endpoints between study groups [33]. Response rates were compared between groups using Fisher's exact tests. Magnitudes of responses among positive responders were compared between study groups using Wilcoxon rank sum tests. All statistical tests were 2-sided. Primary and secondary analyses comparing immunogenicity endpoints between vaccinated groups were considered statistically significant if \( p \leq 0.033 \), chosen to control the overall type I error rate at 0.10 and correcting for three pairwise comparisons. All other analyses used \( p \leq 0.05 \) to judge statistical significance. All descriptive and inferential statistical analyses were performed using SAS and/or R statistical software.

### Results

**Participant accrual, demographic data, and vaccine safety**

Of the 736 individuals who underwent screening procedures, Ad5 and Ad35 neutralizing antibody titers were unavailable for fourteen individuals who underwent Ad35 neutralizing antibody screening. **Table 2:** Frequency and titers of neutralizing antibody to Ad5 and Ad35 among those screening for trial eligibility.

<table>
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<td>Total</td>
<td>736</td>
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*Ad5 neutralizing antibody titers were unavailable for fourteen individuals who underwent Ad35 neutralizing antibody screening.

### HIV-1-specific antibody responses

Each of the vaccine regimens induced high frequency and magnitude cross-clade binding antibody responses (Figure 2). The antibody response rates were 100% for all treatment groups recognizing the consensus M gp140 (data not shown) and 97-100% recognizing the clade A Env antigen. For the clade B antigen, responses were also detected in greater than 92% of individuals. For the clade C antigen, response frequencies were highest for rAd35/rAd5 (96%) compared to the DNA prime/adenovector boost groups (76-78% for groups 2-4), however at lower magnitude in comparison to the DNA/rAd5 group (p=0.02).

Based on evidence that IgG binding antibodies to V1/V2 were correlated with reduced risk of HIV infection in the RV144 vaccine
Figure 1: Safety assessment, showing maximum local reactogenicity A) and systemic reactogenicity, B) by treatment group. Subjects in control (C) groups 1-4 received group phosphate buffered saline. Subjects in treatment groups 1-3 (T1-T3) were Ad5 seronegative at baseline and received: T1- recombinant Ad35 (rAd35) prime and rAd5 boost; T2- three DNA priming injections boosted by rAd5; and T3- three DNA priming injections boosted by rAd35. Subjects in T4 were Ad5 seropositive at baseline and received three DNA priming injections boosted by rAd35. P values for comparisons of local and systemic reactogenicity were determined using the Kruskal-Wallis test.
Figure 2: Binding antibody net responses to Clades A (OOMSA 4076 gp140), B (B.con.env03 140CF), and C (C.con.env03 140CF) isolates 4 weeks after the boost vaccination as measured by median fluorescence intensity (MFI)-Blank where ‘Blank’ is a sample specific background measure. Responders are shown in red circles and non-responders in blue triangles. Box plots display the distribution of positive responses for the vaccinees for each antigen. P-values are derived from Lachenbruch’s test comparing rAd5 and rAd35 boosted groups in Ad5 seronegative individuals and the Ad35-boosted group in Ad5 seropositive individuals.
efficacy trial [8], we explored whether the EnvA constructs tested in HVTN 077 elicited these responses. Among positive responders, all treatment groups elicited gp70V1/V2 responses using the V1/V2 scaffold tested in the RV144 study (Case A2, Figure 3A) and there were no significant differences by group in the magnitude or frequency of the responses. In addition, we looked at the matching clade A V1/V2 sequence in the HVTN 077 vaccine regimen (clade A gp70V1/V2). Although the frequency of response did not differ substantially by group, as seen in Figure 3B, the response magnitude for binding antibodies to the vaccine-matched clade A gp70V1/V2 was significantly higher among the DNA/rAd5 group compared to the rAd35/rAd5 group, (p=0.005).

HIV-1–specific T-cell responses

As seen in Figure 4, HIV-1–specific T cells producing IFN-γ and/or IL-2 in response to vaccine insert-matched peptides were detected readily in each of the treatment groups. With regard to the CD4+ T-cell responses, the highest post-boost response rates were seen among Ad5 seronegative individuals receiving DNA/rAd35 (25/36, 69.4%) and lowest among those receiving rAd35/rAd5 (9/24, 37.5%); responses did not differ significantly across groups. Vaccine-induced CD8+ T-cell responses were elicited most frequently among Ad5 seronegative individuals who received the DNA/rAd5 regimen (32/42, 76.2%) and least among Ad5 seropositives who received the DNA/rAd35 regimen (10/25, 40.0%); responses did not differ significantly across groups. Overall, we found that among Ad5 seronegative subjects, 15%, 39%, and 32% of rAd35/rAd5, DNA/rAd5, and DNA/rAd35 recipients, respectively, and 14% of Ad5 seropositive participants receiving the DNA/rAd5 regimen developed both CD4+ and CD8+ T-cell responses. The HIV-specific CD4+ or CD8+ T-cell response magnitudes for positive responders after boosting were similar across groups.

In addition, we assessed expression of TNF-α and Granzyme B (GzB) in response to stimulation with insert-matched peptides. As shown in Figure 5, priming with DNA followed by either rAd35 or rAd5 led to the induction of significantly more polyfunctional CD4+ T cells than vaccination with rAd35/rAd5 in Ad5 seronegative subjects (p=0.0005 for three and p=0.007 for four functions, respectively, comparing the combined DNA/rAd5 and DNA/rAd35 groups with rAd35/rAd5 for Ad5 seronegative subjects). Interestingly, the patterns of combined expression of these functional markers did not

Figure 3: Binding antibody net responses to A) gp70 V1/V2 (Case A2) used in the RV144 trial and B) gp70 V1/V2 (A), the V1/V2 antigen contained in the VRC A vaccine strain 4 weeks after the boost vaccination as measured by median fluorescence intensity (MFI)-Blank where ‘Blank’ is a sample specific background measure. Responders are shown in red circles and non-responders in blue triangles. Box plots display the distribution of positive responses for the vaccinees for each antigen. P-values are derived from Lachenbruch’s test comparing rAd5 and rAd35 boosted groups in Ad5 seronegative individuals and the Ad35-boosted group in Ad5 seropositive individuals.
Figure 4. HIV-specific CD4+ and CD8+ T-cell responses: The percentage of CD4+ (panel A) and CD8+ (panel B) T cells producing γ-interferon (IFN-γ) and/or interleukin-2 (IL-2) in response to EnvA matched peptide pools 4 weeks after the priming immunization(s) and 4 weeks after the boost as measured by intracellular cytokine staining. Responders are shown in red circles and non-responders in blue triangles. Boxplots show the distribution of the magnitude of response in positive responders only. The box indicates the median and interquartile range (IQR); whiskers extend to the furthest point within 1.5 times the IQR from the upper or lower quartile. Numbers at the top of each panel show the number of responders / number with an assay result and the percent with positive response. P-values are derived from Lachenbruch’s test comparing rAd5 and rAd35 boosted groups in Ad5 seronegative individuals and the Ad35-boosted group in Ad5 seropositive individuals. Data from samples with high background cytokine secretion was filtered, leading to differences in the number of samples with available data for CD4+ and CD8+ T cells.
higher than the 17.5% rate of response elicited by the HVTN 505 regimen tested in the RV144 trial (64%, 95% CI 58% to 70%) [8]. Of note, in HVTN 077, we found the proportion of vaccinees with Nef was unable to prevent HIV acquisition or reduce viral load prime-boost regimen encoding EnvA, EnvB, EnvC, clade B Gag, Pol, which were correlated with reduced risk of HIV infection in the RV144 cross-clade binding antibodies as well as V1/V2-specific IgG antibodies, each of the vaccine regimens tested in this trial was capable of inducing to substantially dampen immunogenicity [23]. Finally, we found that responses from these serologically distinct adenoviruses are unable to findings from preclinical models that cross-reactive immune responses to an Ad35-based regimen when given once as a boost. This was no significant reduction of HIV-1 specific antibody or cellular responses. In addition, we found that in the setting of pre-existing Ad5 nAbs, there was no significant reduction of HIV-1 specific antibody or cellular responses to an Ad35-based regimen when given once as a boost. This confirms findings from preclinical models that cross-reactive immune responses from these serologically distinct adenoviruses are unable to substantially dampen immunogenicity [23]. Finally, we found that each of the vaccine regimens tested in this trial was capable of inducing cross-clade binding antibodies as well as V1/V2-specific IgG antibodies, which were correlated with reduced risk of HIV infection in the RV144 vaccine efficacy trial [8].

The HVTN 505 Phase IIb efficacy trial showed that a DNA/rAd5 prime-boost regimen encoding EnvA, EnvB, EnvC, clade B Gag, Pol, and Nef was unable to prevent HIV acquisition or reduce viral load [7]. Of note, in HVTN 077, we found the proportion of vaccinees with V1/V2 IgG responses (52% to 66% across the four groups) was similar to the rate observed for the partially efficacious ALVAC/gp120 vaccine regimen tested in the RV144 trial (64%, 95% CI 58% to 70%) [8] and higher than the 17.5% rate of response elicited by the HVTN 505 regimen [7]. In addition, the V1/V2 IgG responses were similar between groups 2 and 3 (DNA/rAd5 and DNA/Ad35 in Ad5 seronegative subjects), and group 4 (DNA/rAd35 in Ad5 seropositive subjects). This is in contrast to findings from the phase 2 study of the VRC multiclade DNA/rAd5 regimen [12], where V1/V2 IgG responses were significantly lower in Ad5 seropositive vaccines compared to Ad5 seronegative individuals (G. Tomaras, personal communication). These findings suggest that presentation of the EnvA antigen alone may produce a more favorable antibody response to the V1/V2 region than presentation of multiple Env proteins with additional competing antigens. It is important to note that we do not know if the V1/V2 IgG correlate of risk translates into a correlate of protection, and, if so, whether it is a mechanistic or non-mechanistic correlate [35] or whether IgG V1/V2 responses will be a correlate of HIV-1 risk or protection for vaccines in other populations that differ from the community-based sample evaluated in Thailand [6]. However, studies in non-human primate models suggest that envelope binding antibodies, V2-specific antibodies, and the avidity to which anti-Env antibodies bind to native trimer [18,36-38] can correlate with protection. Therefore, future HIV-1 vaccines designed to elicit Env binding responses and V2-specific IgG antibodies, should consider these observations from preclinical studies and recent clinical trials.

Whether multi-dose DNA priming for an adenovector boost confers an immunologic advantage over heterologous adenovector regimens is relevant given the desire for less complex vaccine regimens with fewer required immunizations. Compared to rAd35/rAd5, we found that the DNA/rAd5 regimen elicited higher magnitude binding antibody responses to some of the antigens tested (e.g., the EnvA clade-matched V1/V2 expressed by the vaccine and EnvC) but not to others (e.g., the clade A Env). And while there was no overall difference in the HIV-specific CD4+ or CD8+ T-cell responses elicited by these regimens, DNA priming may generate more polyfunctional responses than the heterologous adenovector prime-boost regimen, a desirable feature of vaccines designed to elicit cellular immunity [39,40]. Several studies in the field will provide further insights into the relative immunogenicity of prime-boost regimens combining different adenovectors such as...
Ad35 and Ad26 encoding an EnvA antigen (IAVI B003-IPCAV004-HVTN091, NCT01215149) and DNA administered by electroporation with a multi-antigen rAd35 construct (IAVIB004; NCT01496989). Furthermore, to optimize immunogenicity, trials should carefully consider the administration interval between adenovector prime and boost. Our study delivered rAd35 and rAd5 6 months apart, eliciting higher magnitude HIV-specific T-cell responses compared to rAd35/rAd5 given only 3 months apart in VRC’012 (NCT00479999) [22].

Conclusion

In this phase 1b study, we have demonstrated that rAd35 is well tolerated and immunogenic, and as a boost, is as potent as rAd5 in DNA primed individuals. In addition, the humoral and cellular responses elicited by rAd35 boosting are better preserved in the setting of pre-existing Ad5 seropositivity than responses to rAd5 boosting, suggesting that rAd35 is a reasonable choice for an alternative adenoviral vaccine vector to diminish the impact of antivector immunity. Therefore, as additional safety data emerge from studies exploring alternative adenoviral vectors in different global contexts, rAd35 should be considered for use as a vaccine delivery vector, particularly as effective antigen designs become available. This is particularly relevant when CD8+ T cell-mediated immunity is desirable in addition to antibody-based immunity, in subjects already primed with the antigens expressed by the rAd35 vector, and in settings with a high prevalence of pre-existing immunity to Ad5, such as in sub-Saharan Africa.

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Author contributions

Designed the study: JF, PAB, PG, NF, SD, TW, BG*, MJM. Oversaw study conduct and managed participants at study sites: JF, PAB, LB, BK, MS, KM, PG, NR, SK, MK, JMJ. Medical monitoring and study oversight: JF, PAB, ES*, CM, BG*. Oversaw performing immunogenicity assays and result interpretation: JF, NF, SD, SR, GT, JM, BG*. Analyzed the data: JF, NK, PG, NF, GT, BG*, JMJ. Wrote the manuscript: JF, PG, NF, GT, BG, MJM.

*This paper was written by authors in their capacity as NIH employees, but the views expressed in this paper do not represent those of the NIH.

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